UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

Date: January 8, 2003

Subject: **Dicamba** Plasma Kinetics Study in Rats.

Tox. Chem. No.: None
PC Code: 029801
DP Barcodes: D281798
Submission Nos.: S590360
TXR # 0050578

From: P. V. Shah, Toxicologist
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Through: George Herndon, Branch Senior Scientist
Registration Action Branch 1
Health Effects Division (HED) (7509C)

ACTION REQUESTED

The Registration Division has requested that the Health Effects Division (HED) review the rat plasma kinetics study for dicamba, MRID 44609801, in support of registration.

CONCLUSIONS

The Health Effects Division has evaluated the submitted plasma kinetics study in rats for dicamba and provided the Data Evaluation Record (DER). This study is a special study to measure pharmacokinetic of dicamba in rats with limited toxicity measurements included. This study is classified as acceptable/nonguideline study and does not satisfy the guideline requirements (OPPTS 870.7485) for general metabolism in rats.

This memorandum contains the study citations and executive summary of this review. The full data evaluation record (DER) is attached.

RESULTS

Citation

Leibold, E., Hoffmann, H. and Hildebrand, B. (1998) ^{14}C-Dicamba-Study of the Plasma Kinetics in Rats. BASF Aktiengesellschaft, Department of Toxicology, Laboratory Project Identification 02B0266/976009. May 18, 1998. MRID 44609801. Unpublished.

EXECUTIVE SUMMARY: In a plasma kinetics study, (MRID 44609801), [phenyl-U-^{14}C]-dicamba ([^{14}C]-dicamba; 86.0% a.i. radiochemical purity), was administered as a dietary admix to 4 male and 4 female Wistar and Sprague-Dawley at 900, 1500, 3000, 4500, and 12000 ppm (Wistar rats) and 900, 1500, 3000, 6000 and 9000 ppm (Sprague-Dawley rats) for fourteen days, followed by a radioactive dose of 90, 150, 300, 450 mg/kg bw (Wistar rats) and 75, 125, 250, 500 and 800 mg/kg bw by a single gavage dose (in 10 ml/kg body weight 0.5% Tylose CB 30.000 in aqua bidest). Plasma levels were measured at various time intervals following radioactive dose.

A preliminary study in Wistar rats suggests excessive toxicity following repeated gavage doses. Therefore, the main study in both strains of rats was conducted as a dietary ad mix followed by a gavage dose of radiolabeled dicamba. In both strains of rats, the plasma levels reached a maximum level after 0.5-1 hour following the gavage dose and declined thereafter. The AUC $_{0-\infty}$ values were calculated from the plasma concentrations versus time curves at the respective dose levels indicated linear relationship with increase in dose up to a certain dose levels in both strains of rats indicating saturation of excretion. Initial plasma half-life was increased with increasing dose, but terminal half-life remains more or less constant in both strains of rats indicating saturation of excretion. Plasma half-life was increased with increasing dose giving no indication of saturation of oral absorption.

In Wistar rats, the increase in plasma AUC was linear with dose up to a level of 150 mg/kg bw in males and 300 mg/kg bw in females. Above these dose levels, plasma AUC-values increased more than dose. Sprague-Dawley rats showed similar results, with the increase in AUC being linear with dose up to a level of 125 and 250 mg/kg bw in males and females, respectively. Above these dose levels, plasma AUC-values increased more than dose. Considering that oral absorption was not saturated and that initial plasma levels went up with dose, the disproportionate increase in plasma AUC is clearly due to saturation of renal excretion of dicamba resulting in a longer plasma half-life. This is supported by half-life data in both species which showed an increase in plasma half-life with dose.

This plasma kinetics study in the rats is classified **Acceptable/Nonguideline (§85-1).**

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided. Flagging statements were not provided.

EPA Reviewer: P. V. Shah, Ph.D.
Registration Action Branch 1, Health Effects Division (7509C)
EPA Secondary Reviewer: David Nixon, DVM
Registration Action Branch 1, Health Effects Division (7509C)

P.V. Shah, Date 4/11/02
David Nixon, Date 4/11/2002

TXR No. 0050578

DATA EVALUATION RECORD

STUDY TYPE: Pharmacokinetics - [rat]; OPPTS 870.7485 [§85-1, data submitted for dicamba]

DP BARCODE: D281798
P.C. CODE: 029801

SUBMISSION CODE: S590360
TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): Dicamba (86% purity)

SYNONYMS: 3, 6-Dichloro-2-methoxybenzoic acid-[phenyl-U- ^{14}C]

CITATION: Leibold, E., Hoffmann, H. and Hildebrand, B. (1998) ^{14}C-Dicamba-Study of the Plasma Kinetics in Rats. BASF Aktiengesellschaft, Department of Toxicology, Laboratory Project Identification 02B0266/976009. May 18, 1998. MRID 44609801. Unpublished.

SPONSOR: BASF, Research Triangle Park, NC

EXECUTIVE SUMMARY: In a plasma kinetics study, (MRID 44609801), [phenyl-U-^{14}C]-dicamba ([^{14}C]-dicamba; 86.0% a.i. radiochemical purity), was administered as a dietary admix to 4 male and 4 female Wistar and Sprague-Dawley at 900, 1500, 3000, 4500, and 12000 ppm (Wistar rats) and 900, 1500, 3000, 6000 and 9000 ppm (Sprague-Dawley rats) for fourteen days, followed by a radioactive dose of 90, 150, 300, 450 mg/kg bw (Wistar rats) and 75, 125, 250, 500 and 800 mg/kg bw by a single gavage dose (in 10 ml/kg body weight 0.5% Tylose CB 30.000 in aqua bidest). Plasma levels were measured at various time intervals following radioactive dose.

A preliminary study in Wistar rats suggests excessive toxicity following repeated gavage doses. Therefore, the main study in both strains of rats was conducted as a dietary ad mix followed by a gavage dose of radiolabeled dicamba. In both strains of rats, the plasma levels reached a maximum level after 0.5-1 hour following the gavage dose and declined thereafter. The AUC $_{0-\infty}$ values were calculated from the plasma concentrations versus time curves at the respective dose levels indicated linear relationship with increase in dose up to a certain dose levels in both strains of rats indicating saturation of excretion. Initial plasma half-life was increased with increasing dose, but terminal half-life remains more or less constant in both strains of rats indicating saturation of excretion. Plasma half-life was increased with increasing dose giving no indication of saturation of oral absorption.

In Wistar rats, the increase in plasma AUC was linear with dose up to a level of 150 mg/kg bw in males and 300 mg/kg bw in females. Above these dose levels, plasma AUC-values increased more than dose. Sprague-Dawley rats showed similar results, with the increase in AUC being linear with dose up to a level of 125 and 250 mg/kg bw in males and females, respectively. Above these dose levels, plasma AUC-values increased more than dose. Considering that oral absorption was not saturated and that initial plasma levels went up with dose, the disproportionate increase in plasma AUC is clearly due to saturation of renal excretion of dicamba resulting in a longer plasma half-life. This is supported by half-life data in both species which showed an increase in plasma half-life with dose.

This plasma kinetics study in the rats is classified **Acceptable/Nonguideline (§85-1).**

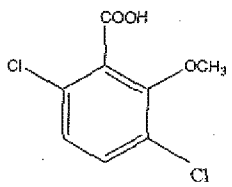
COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided. Flagging statements were not provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Compound:

3, 6-Dichloro-2-methoxybenzoic acid- [phenyl-U-^{14}C]
Radiochemical purity: >95%
Specific activity: 16.3 mCi/mmol
Lot/Batch: 037H9294 (Sigma Chemicals, St. Louis, USA)
Description: solid



Non radioactive dicamba; 3, 6-Dichloro-2-methoxybenzoic acid
Purity: 86 % a.i.
Lot/Batch No.: 52103810
Description: solid
Contaminants: not described
CAS No.: 99387-89-0

2. Vehicle: 0.5% Tylose CB 30.000 in Aqua Bidest as carrier

3. Test animals: Species: Rat
Strain: Chbb-THOM (SPF) Wistar
CRL:CD BR (Sprague-Dawley)
Age and weight at study initiation: At least 7 weeks
Source: Wistar: Boehringer Ingelheim Pharma KG, Biberach a.d. Riss (FRG)
Sprague-Dawley: Charles River Deutschland, Sulzfeld (FRG)
Housing: During acclimatization in type III Macrolon cages; Steel Wire Mesh Cages during pretreatment and during plasma level experiments
Diet: Kliba lab Diet, either pelleted or granulated, *ad libitum*
Water: Tap water, *ad libitum*
Environmental conditions:
Temperature: 20-24° C
Humidity: 30-70%
Air changes: not indicated
Photoperiod: not indicated in report
Acclimation period: not indicated in report

4. Preparation of dosing solutions:

Appropriate amounts of the radiolabeled and unlabeled test material were combined and dissolved in acetone. Acetone was evaporated to dryness at -30° C under vacuum. The residue was suspended in 0.5% Tylose CB 30.000 in aqua bidest and filled up to the final volume in order to achieve the required concentration. The test chemical was then suspended by mixing and sonication prior to administration. Aliquots were removed prior to dosing to determine concentration and homogeneity of the radioactivity. The stability in the carrier (feed, 0.5% Tylose CB 30.000 in aqua bidest) was checked in all experiments. No results of these analyses were provided.

B. STUDY DESIGN AND METHODS:

These studies were designed to determine the plasma levels following pretreatment with dicamba (non radioactive) in diet or gavage for 14 days followed by a radioactive doses and measuring plasma levels at various time points following administration of the radioactive dose. The main study was conducted in both Wistar and Sprague-Dawley rats.

Animals were not randomly assigned to dose groups because similar age animals are required for this study type. Nominal doses for each test group are presented in Table 1.

The in-life portions of these studies were conducted from June, 1997 to November, 1997.

Table 1. Dose groups for [^{14}C] dicamba pharmacokinetic studies

Strain of Rats/dose	Non radioactive dose /Method Administration	Radioactive Dose mg/kg (gavage)	No. of Animals M/F	Remarks
PRELIMINARY STUDY				
Wistar/1000 mg/kg/day	1000 mg/kg/day /gavage for 14 days	1000	4/4	Plasma levels (terminated prematurely)
Wistar/400 mg/kg/day	400 mg/kg/day /gavage for 14 days	400	4/4	Plasma levels (terminated prematurely)
Wistar/150 mg/kg/day	150 mg/kg/day /gavage for 14 days	150	4/4	Plasma levels (terminated prematurely)
Wistar/12000 ppm	12000 ppm/dietary for 6 days	1000 mg/kg non radioactive	2/2	body weight, food consumption, clinical signs and sacrificed in 24 hours after gavage dose

MAIN STUDY				
Wistar/12000 ppm	12000 ppm/dietary for 14 days	800	4/4	plasma levels and microscopic examination of stomach
Wistar/4500 ppm	4500 ppm/dietary for 14 days	400	4/4	plasma levels and microscopic examination of stomach
Wistar/1500 ppm	1500 ppm/dietary for 14 days	150	4/4	plasma levels and microscopic examination of stomach
Wistar/4500 ppm	4500 ppm/dietary for 14 days	450	4/4	plasma levels
Wistar/3000 ppm	3000 ppm/dietary for 14 days	300	4/4	plasma levels
Wistar/1500 ppm	1500 ppm/dietary for 14 days	150.	4/4	plasma levels
Wistar/900 ppm	900 ppm/dietary for 14 days	90	4/4	plasma levels
Sprague-Dawley/9000 ppm	9000 ppm/dietary for 14 days	800	4/4	plasma levels and microscopic examination of stomach
Sprague-Dawley/6000 ppm	6000 ppm/dietary for 14 days	500	4/4	plasma levels and microscopic examination of stomach
Sprague-Dawley/3000 ppm	3000 ppm/dietary for 14 days	250	4/4	plasma levels and microscopic examination of stomach
Sprague-Dawley/1500 ppm	1500 ppm/dietary for 14 days	125	4/4	plasma levels and microscopic examination of stomach
Sprague-Dawley/900 ppm	900 ppm/dietary for 14 days	75	4/4	plasma levels and microscopic examination of stomach

1. Dosing and sample collection

Dose selection was based on previously performed studies on the subacute, subchronic, chronic toxicity studies of dicamba and on the basis of preliminary experiments in this study. For oral radioacive administration, doses selected ranged from 90 to 800 mg/kg for Wistar rats and from 75 to 800 mg/kg for Sprague-Dawley rats. Radioactive dose solution was administered in the carrier (0.5% Tylose CB

30.000 in aqua bidest) at 1 ml/100 gram body weight by gavage. The pretreatment doses for 14 days were administered as a dietary admix using 0.5% Tylose CB 30.000 in aqua bidest as carrier and made available *ad libitum*. At the end of the pretreatment period (14 days), animals were treated with radioactive dicamba and blood samples (100-200 µl) were taken retro-orbitally at the following time points: 0.5, 1, 2, 4, 6, 8, 12, 24 and 48 hours. The weight of the animals were recorded at the begining of the pretreatment period, after one week and prior to radioactive dosing. During the treatment period, food consumption and test substance intake were determined for each animal. Stability and homogeneity was also measured but not reported in the study report. The study report indicates that it demonstrated stability and homogeneity.

2. Sample Preparation

Aliquots of plasma were mixed with scintillation cocktail (Hionic Fluor, Pachard Instrument Co.) and counted for 10 minutes in a liquid scintillation counter (Wallace type 1409) and disintegration rate corrected by the respective background.

3. Statistics

Group means and standard deviations were calculated. Radioactive counts were corrected for quenching and background radiation. Tissue concentration per gram tissue weight was determined. Analysis of kinetic data (calculation of plasma half-life (t1/2) and the Area Under the Curve from t=0 h to infinity ($AUC_{0-\infty}$) was performed based on the group mean values using the PC program system TOPFIT Version 2.0.

II. RESULTS

Preliminary Study: At 1000 mg/kg/day dose level via gavage, all males and one female Wistar rat died within 3 hours after second administration. The remaining animals showed clinical signs of toxicity such as piloerection, squatting posture, convulsions and respiratory sounds. A second female died after third administration and remaining animals were sacrificed thereafter. Macroscopic examination showed thickening of the wall in the forestomach and erosions and ulcerations in the glandular stomach. At 400 mg/kg/day and 150 mg/kg/day via gavage, all animals (Wistar rats) were sacrificed after third administration due to all animals showing clinical signs of toxicity. At 400 mg/kg/day, clinical signs such as piloerection, ataxia and respiratory sounds were reported. At 150 mg/kg/day, ataxia was reported. At 400 mg/kg/day, macroscopic examination revealed thickening of the wall in the forestomach; hyperemia in the glandular stomach in three animals; and erosion/ulceration in one animal. At 150 mg/kg/day, macroscopic examination revealed thickening of the wall in the forestomach in three males and one female and

hyperemia in the glandular stomach in three animals. Preliminary study via gavage clearly indicates excessive toxicity.

In a dietary admix study in Wistar rats, 2 males and 2 females were fed 12000 ppm for six days and a radioactive dose of 1000 mg/kg via gavage, showed unsteady gait after second day feeding onwards. During the feeding period, food consumption was reduced (reduced compound inatke) but body weight was not affected. After radioactive dosing, clinical signs such as piloerection, respiratory sound and unsteady gait increased in severity but no mortality reported. Macroscopic examination revealed thickening of the wall in the forestomach in two males and one female and few erosions/ulcerations in the glandular stomach.

The preliminary study results and individual animal data were not provided in the study report.

Main Study: In one study (Table 2), Wistar rats were pretreated with dicamba at 1500, 4500 and 12,000 ppm for 14 days followed by a radioactive dose of 150, 400, and 800 mg/kg, respectively, by gavage for plasma level measurements. The selected parameters are presented in Table 2. Body weight changes were clearly decreased in high dose (12000 ppm) group. At the high dose, unsteady gait was observed after one week on diet. At sacrifice, a gastric erosion was observed in one animal each of the high and intermediate dose group. Clinical observations and necropsy findings on individual animals were not reported.

In a second study (Table 3), Wistar rats were pretreated with dicamba at 900, 1500, 3000 and 4500 for 14 days followed by a radioactive dose of 90, 150, 300, and 450 mg/kg, respectively, by gavage for plasma level measurements. The selected parameters are presented in Table 3. In this study, there were no effects on body weight or any clinical signs of toxicity. This study was designed to further characterize the saturation of excretion kinetics.

A third study was conducted in Sprague-Dawley rats since most toxicological studies with dicamba were conducted previously. In this study, Sprague-Dawley rats were pretreated with dicamba at 900, 1500, 3000, 6000 and 9000 ppm for 14 days followed by a radioactive dose of 125 ,250, 500, and 800 mg/kg, respectively, by gavage for plasma level measurements. The selected parameters are presented in Table 4. Body weight changes were slightly decreased in both males and females at high dose (9000 ppm) and females of 6000 ppm dose group. After administration of radioactive dicamba, all animals of the two top doses and also the 3000 ppm females showed convulsions and three top dose females and one male of 6000 ppm died prematurely. At sacrifice, no macroscopic findings were observed in the stomach of the animals. Clinical observations and necropsy findings on individual animal were not reported.

Table-2 Selected Parameters in Wistar Rats[a]

Parameters Measured	Males			Females		
	1500 ppm	4500 ppm	12000 ppm	1500 ppm	4500 ppm	12000 ppm
Body Weight, Day 0 (g)	225.1 (5.7)[b]	230.2 (8.0)	226.9 (4.7)	172 (3.6)	171.1 (5.0)	171.3 (4.8)
Body Weight, Day 15 (g)	307.9 (13.1)	323.1 (12.9)	260.9 (9.5)	203 (7.4)	198.1 (6.4)	184 (9.2)
Body Weight Gain (g)[c]	82.8	92.9	34	31	27	12.7
Compound Intake (d 7-14), (mg/kg)	122.7 (2.1)	366.7 (3.6)	988.7 (25.6)	126.9 (10.3)	366.4 (21.2)	1043.9 (22.2)
Dose, Day 15 (mg/kg)	148.2 (1.5)	400.9 (8.5)	910.6 (95.9)	149.7 (1.4)	403.3 (5.1)	832.7 (76.3)

a Data taken from Tables 1-3, Pages 32-34, MRID 44609801. Average Value of 4 rats.
b Value in parenthesis ± SD
c Data calculated by the reviewer.

Table-3 Selected Parameters in Wistar Rats[a]

Parameters Measured	Males				Females			
	900 ppm	1500 ppm	3000 ppm	4500 ppm	900 ppm	1500 ppm	3000 ppm	4500 ppm
Body Weight, Day 0 (g)	229.5 (7.9)[b]	228.6 (8.8)	227.9 (6.5)	228.0 (6.2)	175.6 (8.0)	180.9 (5.0)	177.5 (7.1)	178.4 (4.8)
Body Weight, Day 15 (g)	326.3 (9.3)	317.3 (12.3)	314.4 (18.3)	305.7 (6.3)	203.6 (16.4)	212.2 (7.2)	211.9 (12.9)	220.2 (12.8)
Body Weight Gain (g)[c]	96.8	88.7	86.5	77.7	28.0	31.3	31.0	41.8
Compound Intake (d 7-14), (mg/kg)	73.0 (2.8)	120.1 (6.1)	248.5 (5.3)	369.7 (5.8)	76.8 (2.8)	124.8 (2.1)	247.7 (10.7)	384.0 (16.1)
Dose, Day 15 (mg/kg)	92.6 (1.8)	157.8 (2.7)	313.6 (3.9)	476.0 (10.0)	94.7 (2.6)	158.2 (3.2)	324.5 (6.9)	463.1 (6.5)

a Data taken from Tables 4 - 7, Pages 35-38, MRID 44609801. Average Value of 4 rats.
b Value in parenthesis ± SD
c Data calculated by the reviewer.

Table-4 Selected Parameters in Sprague-Dawley Rats[a]

Parameters Measured	Males					Females				
	900 ppm	1500 ppm	3000 ppm	6000 ppm	9000 ppm	900 ppm	1500 ppm	3000 ppm	6000 ppm	9000 ppm
Body Weight, Day 0 (g)	227.2 (10.8)	229.3 (23.7)	218.7 (17.4)	220.1 (17.2)	225.9 (13.6)	190.8 (8.6)	195.8 (4.7)	193.9 (11.3)	192.4 (12.6)	194.2 (4.1)
Body Weight, Day 15 (g)	348.3 (38.0)	345.8 (35.5)	346.0 (13.6)	365.6 (13.9)	333.6 (30.7)	244.5 (16.7)	253.4 (9.1)	250.1 (26.4)	235.7 (21.0)	231.8 (14.2)
Body Weight Gain (g)[c]	121.1	116.5	127.3	145.5	107.7	53.7	57.6	56.2	43.3	37.6
Compound Intake (d 7-14), (mg/kg)	80.1 (8.7)	126.8 (8.6)	261.7 (16.2)	516.8 (14.7)	726.9 (26.0)	86.3 (3.8)	140.5 (3.6)	262.0 (10.1)	523.6 (17.3)	784.6 (51.2)
Dose, Day 15 (mg/kg)	78.6 (1.1)	128.8 (1.7)	261.1 (5.5)	513.3 (8.7)	841.8 (22.3)	82.4 (2.3)	137.9 (1.8)	253.6 (10.5)	499.4 (7.2)	837.5 (13.4)

a Data taken from Tables 8 -12, Pages 39-43, MRID 44609801. Average Value of 4 rats.
b Value in parenthesis ± SD
c Data calculated by the reviewer.

Plasma Kinetics: Area under the curve (AUC) and plasma half-life following dicamba treatments are shown in Table 5. In one study, Wistar rats were pretreated with dicamba at 1500, 4500 and 12,000 ppm for 14 days followed by a radioactive dose of 150, 400, and 800 mg/kg by gavage reached a maximum plasma level after 0.5-1 hour and declined thereafter. Plasma levels appeared to be increased with increase in dose giving no indication of saturation of absorption. AUC $_{0-\infty}$ values calculated from the plasma concentration versus time curve at the respective dose levels indicated that the AUC increased with increased in dose. However, the increased in AUC does not appear to be linear with the dose. The overall increase in dose from the low to high dose level was 5.3 times; the AUC increased with a factor of 15 in males and 8.2 in females. This may demonstrate saturation of excretion (excretion was not measured), which is indicated by the disproportionate increase of the AUC with increasing dose. Plasma half-lives indicated that the initial half-life increased with the dose, whereas the terminal half-life remained more or less unchanged indicating saturation of renal clearance.

In a second study, Wistar rats were pretreated with dicamba at 900, 1500, 3000 and 4500 for 14 days followed by a radioactive dose of 90, 150, 300, and 450 mg/kg by gavage reached a maximum plasma level after 0.5-1 hour and declined thereafter.

Plasma levels appeared to be increased with increase in dose giving no indication of saturation of absorption. AUC $_{0-\infty}$ values calculated from the plasma concentration versus time curve at the respective dose levels indicated that the AUC increased with increase in dose. However, the increased in AUC does not appear to be linear with the dose. The overall increase in dose from the low to high dose level was 5 times; the AUC increased with a factor of 12.9 in males and 10.0 in females. A deviation from linear relationship between AUC and dose occurred at dose levels above 150 and 300 mg/kg bw in males and females, respectively. The initial plasma half-life is also increased at 300 and 450 mg/kg bw in both sexes.

In a third study, Sprague-Dawley rats were pretreated with dicamba at 900, 1500, 3000, 6000 and 9000 ppm for 14 days followed by a radioactive dose of 125 ,250, 500, and 800 mg/kg by gavage reached a maximum plasma level after 0.5-1 hour and declined thereafter. Similar to Wistar rats, plasma levels increased with increase in dose giving no indication of saturation of absorption. The overall increase in dose from the low to high dose level was 10.7 times; the AUC increased with a factor of 31.1 in males and 41.4 in females. Increase in AUC was not linear with increase in dose. A deviation from linear relationship between AUC and dose occurred at dose levels above 125 and 250 mg/kg bw in males and females, respectively. The initial plasma half-life is also increased at doses above 125 and 250 mg/kg bw in females and males, respectively.

Table 5 Plasma Kinetics in Wistar and Sprague-Dawley Dicamba Treated Rats

Nominal Dose (mg/kg bw	AUC $_{0-\infty}$ (µg Eq*h/g) (increase over previous value)		Half-life in plasma (h)					
			Males			Females		
	Males	Females	Initial Phase	Intermediate Phase	Terminal Phase	Initial Phase	Intermediate Phase	Terminal Phase
Wistar Rats								
150	261	504	1.9	--	13.3	1.2	--	9.7
400 (2.7X)	1504 (5.8X)	1783 (3.5X)	3.5	--	11.8	3.5	--	14.5
800 (2.0X)	3913 (2.6X)	4135 (2.3X)	5.2	--	--	9.4	3.4	8.6
Overall (5.3X)	(15X)	(8.2X)						
Wistar Rats								
90	168	260	2.1	--	15.0	1.0	--	10.8
150 (1.7X)	365 (2.2X)	565 (2.2X)	0.9	3.9	16.8	1.4	--	11.3

300 (2.0X)	1005 (2.8X)	1364 (2.4X)	2.6	--	9.4	4.8	1.3	9.4
450 (1.5X)	2167 (2.2X)	2593 (1.9X)	5.4	--	--	6.0	1.6	6.8
Overall (5.0X)	(12.9X)	(10.0X)						
Sprague-Dawley Rats								
75	111	115	1.3	5.7	32.6	1.5	6.2	18.6
125 (1.7X)	185 (1.7X)	197 (1.7X)	2.1	--	17.2	0.7	3.5	15.1
250 (2.0X)	637 (3.4X)	390 (2.0X)	2.8	1.1	10.5	1.7	--	13.3
500 (2.0X)	2057 (3.2X)	1606 (4.1X)	7.2	3.9	11.3	4.4	1.8	8.6
800 (1.6X)	3447 (1.7X)	4763 (3.0X)	12.4	3.3	9.2	Plateau 1.9	4.6	13.3
Overall (10.7X)	(31.1X)	(41.4X)						

Data taken from Pages 25-28, MRID 44609801

III. DISCUSSION

A. Investigator's Conclusions - In both strains of rats, initial plasma levels and AUC values increased with increasing dose indicating that oral absorption was not saturated in the range of dose tested. In Wistar rats, the increase in plasma AUC was linear with dose up to a level of 150 mg/kg bw in males and 300 mg/kg bw in females. Above these dose levels, plasma AUC-values increased more as dose increased. Sprague-Dawley rats showed similar results, with the increase in AUC being linear with dose up to a level of 125 and 250 mg/kg bw in males and females, respectively. Above these dose levels, plasma AUC-values increased more as dose increased. Considering that oral absorption was not saturated and that initial plasma levels went up with dose, the disproportionate increase in plasma AUC is clearly due to saturation of renal excretion of dicamba resulting in a longer plasma half-life. This is supported by half-life data in both strains which showed an increase in plasma half-life with dose. In summary, saturation of excretion was demonstrated at doses above 150 and 300 mg/kg bw for male and female Wistar rats, respectively and above 125 and 250 mg/kg bw in male and female Sprague-Dawley rats, respectively.

B. Reviewer's Discussion: In the preliminary study at 1000 mg/kg/day dose level via gavage, all males and one female Wistar rat died within 3 hours after second

administration. The remaining animals showed clinical signs of toxicity such as piloerection, squatting posture, convulsions and respiratory sounds. Macroscopic examination showed thickening of the wall in the forestomach and erosions and ulcerations in the glandular stomach. Clinical signs of toxicity were also observed at 400 and 150 mg/kg/day dose levels via gavage. Preliminary study via gavage clearly indicates excessive toxicity.

In a dietary admix study in Wistar rats, 2 males and 2 females were fed 12000 ppm for six days and a radioactive dose of 1000 mg/kg via gavage, showed unsteady gait after second day feeding onwards. During the feeding period, food consumption was reduced (reduced compound intake), but body weight was not affected. After radioactive dosing, clinical signs such as piloerection, respiratory sound and unsteady gait increased in severity but no mortality was reported. Macroscopic examination revealed thickening of the wall in the forestomach in two males and one female and few erosions/ulcerations in the glandular stomach. The dietary study suggests lower toxicity. Therefore, for the plasma kinetics study, dietary route of administration and lower doses were selected.

In one study, Wistar rats were pretreated with dicamba at 1500, 4500 and 12,000 ppm for 14 days followed by a radioactive dose of 150, 400, and 800 mg/kg by gavage reached a maximum plasma level after 0.5-1 hour and declined thereafter. Plasma levels appeared to be increased with increase in dose giving no indication of saturation of absorption. $AUC_{0-\infty}$ values calculated from the plasma concentration versus time curve at the respective dose levels indicated that the AUC increased with increase in dose. However, the increase in AUC does not appear to be linear with the dose. The overall increase in dose from the low to high dose level was 5.3 times, the AUC increased with a factor of 15 in males and 8.2 in females. This may demonstrate saturation of excretion (excretion was not measured), which is indicated by the disproportionate increase of the AUC with increasing dose. Plasma half-lives indicated that the initial half-life increased with the dose, whereas the terminal half-life remained more or less unchanged indicating saturation of renal clearance. In a second study, Wistar rats were pretreated with dicamba at 900, 1500, 3000 and 4500 for 14 days followed by a radioactive dose of 90, 150, 300, and 450 mg/kg by gavage reached a maximum plasma level after 0.5-1 hour and declined thereafter. $AUC_{0-\infty}$ values calculated from the plasma concentration versus time curve at the respective dose levels indicated that the AUC increased with increase in dose. However, the increase in AUC does not appear to be linear with the dose. The overall increase in dose from the low to high dose level was 5 times; the AUC increased with a factor of 12.9 in males and 10.0 in females. In a third study, Sprague-Dawley rats were pretreated with dicamba at 900, 1500, 3000, 6000 and 9000 ppm for 14 days followed by a radioactive dose of 125 ,250, 500, and 800 mg/kg by gavage reached a maximum plasma level after 0.5-1 hour and declined thereafter. Similar to Wistar rats, plasma levels increased with increase in dose giving no indication of saturation of absorption. The overall increase in dose from the low to high dose level was 10.7 times; the AUC

increased with a factor of 31.1 in males and 41.4 in females. Increase in AUC was not linear with increase in dose.

In summary, saturation of excretion was demonstrated at doses above 150 and 300 mg/kg bw for male and female Wistar rats, respectively and above 125 and 250 mg/kg bw in male and female Sprague-Dawley rats, respectively. The measurement of urinary excretion data would have been useful to see whether the saturation of excretion indeed occurred at the dose levels tested. Overall, this study clearly demonstrated a disproportionate increase in AUC with increase in dose.

This study is classified as **Acceptable/Nonguideline (§85-1, Tier 2)**.

C. Study deficiencies - (1) There were no summary or individual data presented for clinical signs in any of the animals tested. Since the purpose of the study is to evaluate plasma kinetics following dicamba treatment, this deficiency is not expected to significantly affect the outcome of the results. (2) Data on the stability of dicamba in carrier were not provided in the study report. However, the study report states that stability and homogeneity were measured. This data may be required to be submitted at a later date. This is not expected to significantly affect the outcome of the study. (3) Purity of non-radioactive dicamba was only 86%. It may affect the results, but is not expected to drastically alter the conclusions. (4) Environmental conditions were not reported